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Meningococcal serogroup Y emergence in Europe

Update 2011

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***Neisseria meningitidis* is differentiated into 12 distinct serogroups, of which A, B, C, W-135, X and Y are medically most important and represent an important health problem in different parts of the world. The epidemiology of *N. meningitidis* is unpredictable over time and across geographic regions. Recent epidemiological surveillance has indicated an increase of serogroup Y invasive meningococcal disease in some parts of Europe as shown in the epidemiological data for 2010 from various European countries previously published in this journal.[1] Here, data is reported indicating that the emergence of serogroup Y continued in 2011 in various regions of Europe. The average age of persons affected by *N. meningitidis* serogroup Y seems to have decreased in some countries in comparison to the previous decade.**

Keywords: epidemiology, Europe, meningococcal disease, serogroup Y, surveillance

Abbreviations: IMD, invasive meningococcal disease; LCCD, late complement component deficiencies; Men, meningococcal

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Introduction

N. meningitidis (meningococcus) continues to cause substantial rates of illness and death worldwide. The incidence of invasive meningococcal disease (IMD) is highest in infants and young children, but there is a second peak of disease among adolescents and young adults. Six immunologically distinct serogroups of *N. meningitidis* (A, B, C, W-135, X and Y) have been associated with significant pathogenic potential and can cause serious invasive disease.[2] Both the incidence and the distribution of disease-causing serogroups vary over time and geographical location.[3-5] Although disease caused by serogroup X has been documented in Africa, it is not a common cause of IMD in other parts of the world.[6] Worldwide, over 90% of IMD is caused by serogroups A, B, C, Y and W-135.

A notable feature of meningococci is their fluctuating epidemiology. There are substantial cyclical fluctuations in the incidence of IMD and the occurrence of outbreaks and epidemics. Currently, nearly 30 European countries provide annual reports on the epidemiology of IMD to the European Centre for Disease Prevention and Control (ECDC).[7] In 2009, the latest year for which data are available from ECDC, the mean incidence of IMD in Europe was 0.92 per 100,000 population, predominantly affecting children younger than 5 y of age, among whom incidence was 7.38 per 100,000, followed by the 15–34 y age group with an incidence of 1.44 per 100,000.[7]

Country specific incidence rates and serogroup and age distributions provide important information for the public health authorities to determine optimal national immunization policies against IMD. Various meningococcal conjugate vaccines based on capsular polysaccharides have been developed, including monovalent serogroup A and C vaccines, and quadrivalent ACWY vaccines. These vaccines are used according to the regional epidemiological situation and serogroup

distribution. Due to the increase in serogroup C disease in Europe during the previous two decades, serogroup C vaccine is currently recommended for immunization of young children in several European countries,[8] while in the USA and Canada, the quadrivalent meningococcal vaccine is used for routine immunization of adolescents. Serogroup A conjugate vaccine has recently been implemented in sub-Saharan countries in Africa to combat devastating and unpredictable meningococcal epidemics that occur at the so-called African meningitis belt. The polysaccharide vaccine approach is not possible for serogroup B, but two recombinant protein-based vaccines for targeting serogroup B isolates are currently undergoing extensive clinical testing and are expected to be soon registered by the regulatory authorities.[9-12] For travelers and people at high risk for IMD, MenACWY conjugate vaccines will replace the plain polysaccharide vaccines and are especially recommended for pilgrims to the Hajj.[13]

During the past decades, changes in serogroup Y disease epidemiology have been reported in North and South America. Since the mid 1990s, the incidence of serogroup Y IMD has been increasing in the USA and it now accounts for more than one third of IMD cases.[3] In Colombia, the proportion of invasive serogroup Y isolates increased from 0% in 1994 to 50% in 2006.[14] In the Northern regions of Mexico, serogroup Y accounted for 26% of all confirmed pediatric IMD cases between 2005 and 2012.[15]

Until recently, serogroup Y has been of minor importance in Europe, accounting for approximately 2% or less of reported IMD cases.[16] Recently, an increase in both absolute numbers and relative proportion of serogroup Y cases has been reported in various European countries for 2010.[1] At the moment, it is difficult to predict whether this rising trend in serogroup Y IMD will continue or if it represents only a short-term rise that will be followed by a reduction in disease rates to the previous relatively low levels. The longevity of the epidemics can vary by the serogroup. The epidemic caused by a certain clone of serogroup B meningococcus lasted for more than a decade in Norway.[17] On the other hand, relatively short emergences of IMD caused by certain serogroups have also been observed. For example, in Greece, the relative proportion of serogroup A suddenly increased in 2000/2001 which was followed by a swift decline in disease levels in the following years.[18] The alarming emergence of serogroup C in 1990s and 2000s in several European countries has effectively been combatted by implementation of routine serogroup C conjugate vaccination, first in the UK[19] and then in several other European countries.[8] Here, we report epidemiological data on serogroup Y IMD in Europe in 2011 collected by various national reference laboratories by their locally established surveillance methods.

Results

Until the 21st century, serogroup Y IMD was rare in Europe, accounting for approximately 2% or less of the cases in most countries and occurring most commonly in elderly patients in association with invasive pulmonary infections or in younger persons with complement component deficiencies. Over the last few years, an increase in the total number of serogroup Y cases as well as in the relative proportion of this serogroup in relation to the other serogroups (A, B, C and W-135) causing IMD has been noted in various regions of Europe. In recently published data for 2010,[1] the highest relative proportion of serogroup Y IMD was reported from the Scandinavian countries (21–39%), followed by the most central/Western European countries (5–10%) and the edges of Europe (West, South-West, East) where the relative proportion has been the lowest (< 5%).

The absolute number and relative proportion of serogroup Y cases in 2011 and the relative proportion in 2010 are presented in **Figure 1** for the 23 European countries from where data were available. Similar to 2010, the relative proportion of serogroup Y cases remained at a high level in several countries as compared with data from 2006. Scandinavian countries and Switzerland still reported the highest serogroup Y disease rates, up to > 55% of all IMD cases in Norway. As compared with 2010, the relative proportion of serogroup Y cases increased significantly in Norway (31% in 2010 to 55% in 2011) and Sweden (39% in 2010 to 51% in 2011), while in Finland, there was a reduction in serogroup Y IMD from 38% in 2010 to 20.6% in 2011. In the Netherlands, the proportion of serogroup Y IMD rose from 8% in 2010 to 17% in 2011, in England and Wales from 7.5% to 9.8% and in France, from 5.5% to 8.7%. In Central European (Austria, Czech Republic, Germany and Poland) and in South European countries (Greece, Italy and Spain), the data for 2011 was similar to that in 2010, with the exception of Malta, Portugal and Slovakia, where the serogroup Y disease rates increased from 0% in 2010 to 27% in 2011, from 0% to 10.4% and from 0% to 12.5%, respectively. In Denmark, Iceland, Scotland, Hungary, Ireland and Lithuania, the proportion of serogroup Y disease remained at the previous low levels.

The mean age of serogroup Y patients is changing in some European countries compared with data from 2006. The average patient ages for 2011 in 9 of the reporting countries are shown in **Table 1**. In the past, predominantly older persons have been affected by this serogroup. A decline in average age was observed in several countries, most prominently in France and Portugal with mean ages of 20 y and 15.5 y, respectively, while in Malta, the mean age was high (60 y). Data on case fatality rates were available for only a few countries and are not shown as it is too early to draw hard conclusions until reports in question are finalized and the significance is not clear due to the low absolute number of IMD cases in most countries. The phenotypic and genotypic characterization of the serogroup Y isolates is ongoing in the participating countries. One particular clone, Y:P1.5–2,10–1,36–2:F4–1:ST-23 (cc23), seems to expand to a variable extent. In Sweden, 25 of the total of 31 serogroup Y meningococci isolated in 2011 belonged to this clones whereas in the other countries the isolates were more heterogeneous.

Discussion

The continuing increase of MenY disease in Europe has important public health implications and will require close

Country	Number of serogroup Y cases, 2011	Relative proportion 2011	Relative proportion 2010
Austria	3	4.4%	5%
Czech Republic	2	3.1%	6%
Estonia	0	0%	0%
Greece	0	0%	0%
Hungary	0	0%	0%
Iceland	0	0%	0%
Ireland	1	1.2%	0%
Lithuania	0	0%	0%
Luxemburg	ND	ND	ND
Poland	2	0.7%	2%
Scotland	2	3.7%	2.3%
Spain	4	0.9%	1%
Belgium	4	4.2%	4.2%
Denmark	5	5.9%	6%
England & Wales	91	9.8%	7.5%
France	43	8.7%	5.5%
Germany	20	7%	7%
Finland	7	20.6%	38%
Italy	16	10.9%	10%
Malta	3	27%	0%
Netherlands	15	17%	8%
Norway	21	55%	31%
Portugal	7	10.4%	0%
Slovakia	2	12.5%	0%
Sweden	31	51%	39%
Switzerland	13	22%	21%

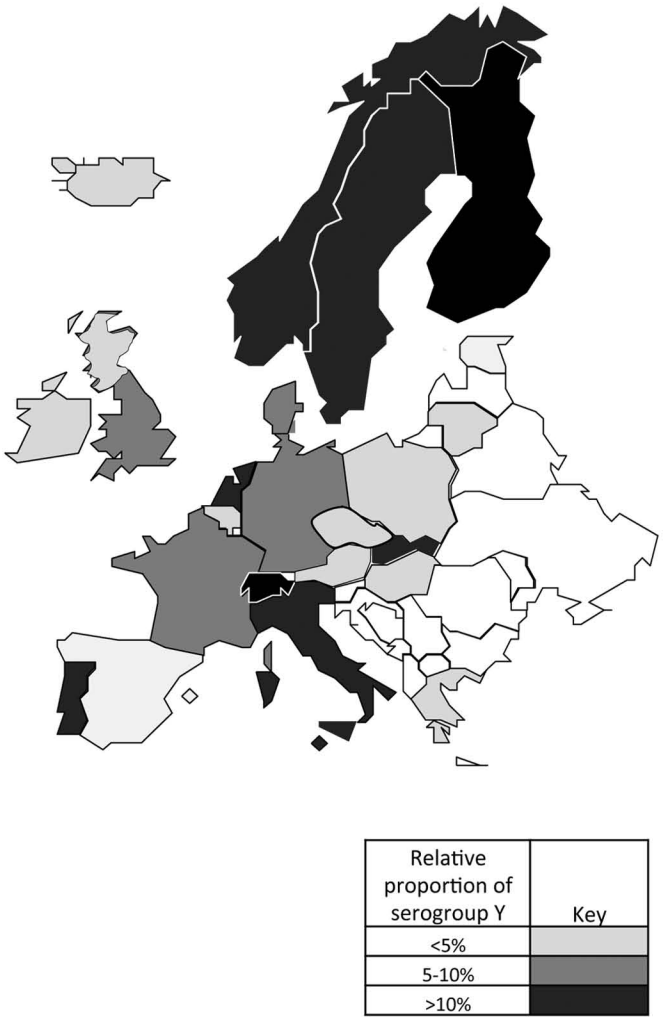

Figure 1. Relative proportion of *N. meningitidis* serogroup Y in various European countries in 2011. The figure is based on data communicated by the scientists listed in the Acknowledgment and/or published in web pages of national public institutes.[20] The data for 2011 are compared with data from 2010, which have been communicated earlier.[1] Color coding refers 2011 data. For Luxemburg, two IMD cases were reported in 2011, of which the serogroups were not determined (ND). Data were not available to the authors for countries shown in white.

monitoring. However, it is worth noting that not all the data presented in the current study have been collected based on the same types of case definitions and surveillance methods and local methodological differences may affect overall results. These and additional epidemiology data should be analyzed carefully, especially in countries with small populations or low IMD incidence because a few cases can have a large impact on findings. For example, in Malta, with a population of less than 500,000 inhabitants and a total of 11 IMD cases in 2011, three serogroup Y cases resulted in a relative proportion of 27%; however due to the small number the importance of this should not be overemphasized. The reason for the shift in meningococcal serogroup distribution in some European countries remains unknown. However, data on possible immune deficiencies (mainly LCCD) are needed especially from the adolescent and young adult age groups as the average age of the first episode of IMD is 17 y.[21]

A careful phenotypic and molecular characterization of the currently circulating serogroup Y isolates in comparison to bacteria isolated before the emergence of this serogroup could reveal the genetic differences that have allowed these strains to spread and escape from population immunity. In an effort to identify possible factors responsible for the emergence of serogroup Y in the United States in the 1990s,[22] a whole genome pyrosequencing was used to investigate genetic differences between serogroup Y strains belonging to the ST-23 clonal complex circulating in early 1990s compared with those circulating during the emergence of serogroup Y later in 1990s. Although the authors found a preponderance of antigens unchanged, they also identified differences in a number of loci that contributed to the antigenic profile of the isolates and may have been responsible for the expansion of serogroup Y disease. Notably, two proteins that have been identified as possible targets for vaccines for the prevention of serogroup B disease - factor H binding protein (fHbp) and Neisserial Heparin Binding Antigen (NHBA)[12]—were highly conserved in these strains.

Table 1. Age distribution of IMD cases caused by serogroup Y from various European countries in 2011

Country	Average age
Denmark	26.0
France	20.0
Italy	26.9
Malta	60.0
Portugal	15.5
Spain	31
Country	**Absolute number of cases in relation to age**
Sweden	9, < 30 y
	9, 30–59 y
	13, > 60 y
The Netherlands	6, ≤ 19 y
	5, 20–49 y
	5, ≥ 50 y
Czech Republic	1, 35 y
	1, 59 y
Slovakian Republic	1, 33 mo
	1, 43 y

The emergence of serogroup C in 1990s–2000s in Europe was successfully arrested through the implementation of monovalent serogroup C conjugate vaccination. In the UK, the control of a meningococcal serogroup C epidemic was accomplished through an expanded vaccination campaign starting in November 1999 and including the expansion of the immunization schedule also to older children and adolescents, thereby reducing carriage rates to providing adequate herd immunity effects, and through the use of catch-up campaigns to ensure high rates of vaccine coverage.[8] Currently, two quadrivalent meningococcal serogroup ACYW conjugate vaccines have been licensed by the European Medicines Agency and can be used if deemed appropriate by public health authorities. Recently, some European countries (e.g., Austria, Czech Republic and Poland) recommended quadrivalent meningococcal vaccine for routine vaccination of adolescents, both for boosting after priming with meningococcal C conjugate in infancy/early childhood but also for primary immunization of individuals who have not received serogroup C vaccine earlier. Meningococcal vaccine schedules are more variable across countries in comparison with vaccines used to protect against other encapsulated bacteria like *Haemophilus influenzae* type b or *Streptococcus pneumoniae*. Country-specific routine recommendations may target infants, older children, adolescents, or some combinations of these. Vaccination policy for IMD, as for most infectious diseases, is determined by the burden of disease, public awareness of the problem, the availability of appropriate vaccines and the ability to fund vaccination campaigns. The efficient prevention of meningococcal disease requires vaccination of a large proportion of the community.[23] The question of whether the apparent increase in serogroup Y disease will continue and requires expansion of vaccine coverage beyond serogroup C as a routine vaccination in Europe or whether vaccination against serogroup Y should be targeted to high risk groups only (e.g., for travelers, people with complement component deficiencies or asplenia), was discussed in a recent editorial.[24] A prerequisite for a broader use of quadrivalent conjugate is that the immune response to the serogroup C component of the quadrivalent vaccine is not inferior to the currently used monovalent serogroup C conjugates which are able to induce a herd immune effect. In Europe, there is yet no quadrivalent meningococcal vaccine that is licensed for children under 1 year of age, whilst in the USA, a quadrivalent meningococcal conjugate vaccine and a Hib/MenCY combination vaccine have been licensed for use in infants. Finally, the decision to use meningococcal vaccines depends on many factors, one of which is economic analysis that has to be done on a regional level.

Disclosure of Potential Conflicts of Interest

M.B. is full-time employee of Novartis Vaccines and Diagnostics, a manufacturer of various meningococcal vaccines. D.P. has received grants from GlaxoSmithKline, Novartis Vaccines and Pfizer to attend scientific meetings. A.S. has received assistance to attend scientific meetings and honoraria for lecturing and her laboratory has received research funding from GlaxoSmithKline, Novartis and Wyeth/Pfizer. The other authors have no conflict of interest to declare concerning this work.

The authors alone are responsible for the views expressed in this publication and do not necessarily represent the decisions, policy or views of the institutes or the company.

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Authors' contributions

M.B. drafted the outline of the manuscript. All authors were actively involved in reviewing the content and editing the text of the manuscript. All authors read and approved the final version of the manuscript.

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